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An MD&DI June 1998 Column

R&D HORIZONS

The Light Stuff: Optical Imaging in Medical Diagnosis

Optical science may light the way to radiation-free tissue analysis.

Greg Freiherr

Somewhere between shadow and light may be answers about whether tissues are diseased or healthy and whether treatment succeeds or fails.

These answers, if they come, will be derived through optical biopsies, a fringe technique that uses visible or near-infrared light to examine in vivo tissue. The technology promises more accurate, safe, and painless diagnoses of eye and heart diseases, melanoma, and lung or breast cancer. It may even open a window to the very foundation of human thought—the place where visual images and short-term memory form.

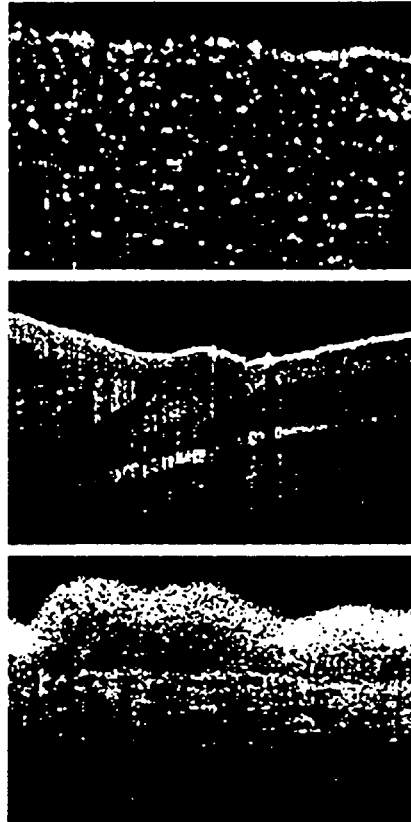
Among the leading technologies, two stand out—optical coherence tomography (OCT) and diffusion imaging. OCT can penetrate only a few millimeters of tissue but can deliver resolution down to a few microns. Diffusion imaging can reach much deeper, providing images of the breast or brain, for example, but it achieves resolution somewhat less than the 50 to 160 μm achieved by conventional mammography and radiography. Both have the advantage of assisting diagnoses without ionizing radiation.

OPTICAL COHERENCE TOMOGRAPHY

The mecca of OCT research is the MIT Research Laboratory of

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Electronics (Cambridge, MA), where James G. Fujimoto, PhD, first developed the concept in 1991. Since then, Fujimoto and his colleagues have developed three general scenarios in which OCT might be clinically valuable. "The first is when standard biopsy is hazardous or impossible to perform," he says. "Second is when standard excisional biopsy has unacceptable false-negative rates—such as in cancer screening when you are looking for very early neoplastic changes. Third is in guiding surgical intervention, such as when you cannot see beneath the surface of tissue or you are looking at the microstructures of nerve."



An OCT scanner took these cross-sectional images of a cucumber slice (top), a human fingernail (middle), and a porcine bladder wall (bottom).

OCT works like ultrasound, generating images from echoes. But, rather than sound, the echoes are waves of light—emitted initially by a laser—that bounce off biological microstructures several millimeters deep in the tissue. A computer converts the returned signals into cross-sectional images by measuring the delay in the echoes. "The advantage over ultrasound is that we have a resolution that is one to two orders of magnitude higher," says Fujimoto. "The limitation of the technique is that light is scattered by most biological tissues, so the penetration depth is limited to 2 to 3 mm."

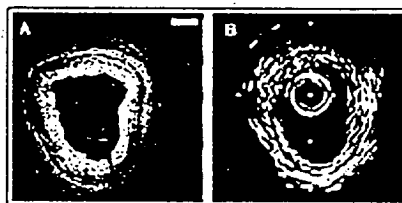
Endoscopes, laparoscopes, and catheters could overcome the penetration problem, allowing application of OCT to tissues deep inside the body. In this scenario, light beamed through fiber optics in a catheter or scope would bounce off the surface of internal tissue. Photons scattered by the tissue would return through the fiber optics to an interferometer, which would divide the light into

reference and sample beams. Interference of the two beams would determine axial resolution. By scanning the signal laterally, OCT would provide a 2-D cross-sectional image.

IMAGING ARTERIES

Working with Mark Brezinski, MD, PhD, at the Massachusetts General Hospital and Harvard Medical School, the MIT group is exploring the use of OCT for cardiovascular, pulmonary, urinary, and gastrointestinal applications. Recent animal and in vitro studies have been notably successful in demonstrating the ability of OCT to assess cardiovascular tissue. Using a fast-scanning OCT system powered by a 200-mW chromium-doped forsterite laser, the research team created real-time in vivo images in animals. Images were captured at four frames per second with better than 10- μ m resolution. Another study focused on the microstructure of atherosclerotic plaque in excised human coronary arteries. Comparison images of the same artery made with an intravascular ultrasound transducer confirmed the clinical potential of this technique. This early study was conducted on excised coronary arteries, but the images were made with the same catheter and fiber optics that would be used in vivo.

The clinical value of OCT was first proven in ophthalmology. In the hands of researchers at the New England Eye Center and Tufts University School of Medicine (Boston), OCT was evaluated in more than 5000 patients. The technique proved useful in detecting early disease progression for a wide range of retinal disease, including diabetic retinopathy and glaucoma. It has since been transferred to private industry as the Humphrey OCT Scanner from Humphrey Systems (San Leandro, CA). The noncontact and noninvasive exam produces high-quality images with resolution to 15 μ m, quantifying the thickness of retinal and nerve-fiber layers to better than 11 μ m.



The OCT image (left) of the human coronary artery provides better resolution than the (right) ultrasound (courtesy of MIT and Circulation).

Researchers at Carnegie Mellon University's Science and Technology Center (Pittsburgh) are helping to push back the frontiers of this new science even further. The center, supported by the National Science Foundation, has conducted both in vitro and in vivo studies of biological tissues. Led by acting director Daniel L. Farkas, PhD, the research team has demonstrated the ability of OCT to show microstructural differences among various types of living tissues. Most important, the team has documented the potential of this technology to diagnose superficial lesions

potential of this technology to diagnose superficial lesions noninvasively—particularly skin lesions such as melanoma. The technology could also provide a means for monitoring wound healing. "OCT is a reflectance measurement, so you get signals from any area that has a big difference—a big transition—in the refractive index," Farkas says.

DIFFUSION IMAGING

The benefits to be derived from diffusion imaging are farther away, yet the major applications—optical mammography and brain imagery—do more to excite the imagination than the superficial exams possible with OCT. Britton Chance, PhD, Eldridge Reeves Johnson professor emeritus of biophysics, physical chemistry, and radiologic physics at the University of Pennsylvania (Philadelphia), is a pioneer in the field of diffusion imaging. Chance has used picosecond-long bursts of near-infrared light to image breast cancer as well as hemorrhages and tumors deep within the brain.

The research is based on the fundamental concept that light passing through the body gathers clues about the tissues through which it passes. Chance has applied this concept to the visualization of brain function, using optical properties to highlight increased cellular activity. For these studies, he and his colleagues constructed a PC-driven device that fires laser pulses received by low-cost diodes, all mounted on a sponge-rubber pad that wraps around the head. "The skull is a very good transmitter of photons," says Chance. "It doesn't have much blood in it, so you don't lose much. We have found that you actually get better signals with the skull in place than with the skull off."

Like OCT, diffusion imaging captures photons that bounce off living cells. Tumors show up well in optical imaging for two reasons. First, they are generally accompanied by a fairly large vascular bed, full of blood, which has a distinct optical signature. Second, they are very hungry for oxygen, which means they take it out of the blood. "We can read out these two kinds of signals, which I call angiogenesis and hypermetabolism, as blood volume and deoxygenated blood," Chance explains.

These same two parameters provide the basis for gauging brain function, because cellular activity is accompanied by an increase in blood flow and deoxygenation of the blood. Chance and his colleagues generated images of brain centers involved in visual imagery, short-term memory, and reading in 350 healthy teenagers. The scanner is now being used in collaboration with researchers at Johns Hopkins to study the brains of schizophrenics.

MIGRATION PATTERNS

Detecting early signs of cancer with light is the goal of researchers

at the Photon Migration Laboratory at Purdue University (West Lafayette, IN) who are trying to develop a light-based system that could penetrate the human breast and differentiate between normal and cancerous tissue. The result so far is a process known as photon migration imaging. The frequency-domain technology illuminates tissue with near-infrared light from a laser diode and then uses an image intensifier and CCD camera to record phase-shift and amplitude modulation at various frequencies. The research has focused on measuring the distribution of picosecond times-of-flight of photons that cross several centimeters of target samples—in vivo and ex vivo tissue as well as latex suspensions and lipid emulsions approximating the consistency of the breast.

Initially, the hope was that normal and diseased tissues would have clearly different optical properties. Such measurements theoretically could provide the data needed to algorithmically reconstruct tomographic images in which diseased tissue would stand out. To establish a reference base for making such distinctions, the Purdue group logged the optical properties of more than 100 histologically classified breast-tissue specimens—both healthy and malignant—searching for optical signatures unique to cancer. Differences were found in the scattering coefficients between cancerous and normal tissue, but those differences spanned a range of values.

"When we looked at the big picture, looked at many different samples, there was a lot of variation. It wasn't clear whether we could ever say that one particular value would indicate disease and another would not," says Jeffery S. Reynolds, PhD, research engineer in the Photon Migration Lab.

The research team looked for help from biocompatible fluorescent chemicals that absorb and then re-emit laser light. Fluorescence might work in optical mammography because breast tumors, like those of other cancers, tend to surround themselves with a bed of blood vessels, which provide the nutrients needed to feed the rapid growth of the malignancy. These vascular beds, perhaps because of their rapid and disorganized spread, are imperfectly formed. As such, they tend to leak fluids into the surrounding tissue. Blood vessels that feed normal tissues do not. Although rapidly cleared from the circulatory system, the fluorescent chemicals envisioned for use in optical mammography would leak into tissue surrounding the breast tumor and stay there long enough to create, in essence, a fluorescent signature specific to cancer.

"In our preliminary work, we have been able to see the re-emitted light that comes from a fluorescent signal," says Reynolds, adding that the use of a contrast agent is not unusual in medical imaging. "Look at any other imaging modalities used diagnostically—x-ray, MRI—and they sometimes use contrast agents to enhance the

specificity of the diagnostic image." The Purdue group is not alone in its belief that fluorescent chemicals may improve the accuracy of optical mammography. For example, a machine prototype built by Philips Medical Systems (Best, Netherlands) uses continuous-wave optical mammography to produce 3-D images of breast tissue. To create those images, Philips researchers applied a fluorescent chemical that re-emitted light.

PHOTON SCANNING

But these fluorescent chemicals, while undeniably helpful, might not be essential. Engineers at Imaging Diagnostic Systems, Inc. (Fort Lauderdale, FL), have constructed a device that generates images of the breast with nothing more than photons.

The company has built a scanner, called the computed tomography laser mammography (CTLTM) system, that acquires data without presenting a hazard to the patient. The CTLTM system fires pulses of light at a wavelength of about 800 nm lasting less than a picosecond. The light, delivered by a diode-pumped laser, is absorbed and scattered by the breast, with emerging photons gathered into contiguous slices by computer. The slices, each 4 mm thick, are then assembled to provide a nearly 3-D view of the breast and its internal structures. Comparisons between these optical mammograms and images made with conventional x-ray mammography and diagnostic ultrasound indicate that the technology might one day be similarly useful in diagnostic settings.

According to Linda B. Grable, president of Imaging Diagnostic Systems, this approach to optical mammography promises to have a higher specificity to cancer than conventional mammography and would serve to reduce the number of unnecessary biopsies. Proving this potential, however, has been difficult. Early clinical studies at a medical center were terminated, according to Grable, because the company was concerned that the behavior of the staff was not consistent with FDA policy. "We have to be very careful with FDA," she says.

FDA has allowed the company to conduct the next series of studies at its manufacturing site, where physicians and biophysicists will operate the device on human volunteers. If these studies are successful, the company will conduct full-scale clinical trials at medical centers in Miami, Chicago, and Los Angeles. In the meantime, engineers will be striving to improve scanner performance. "The biggest challenge we have now is mostly on the software side," says Grable. "We have to clean up the noise."

The Purdue team is facing similar challenges as they move into animal and, later, clinical testing of their mammography device. The biggest problem for ensuring image quality will be handling

the individuality of the patients, Reynolds says. "We know we can reconstruct a simulated tumor in a nice uniform laboratory phantom," he says, "but when you move into the clinical environment, the background changes independently of the disease—and those changes may be greater than the disease change. You have to work very hard at matching your experimental setup to the geometry of the problem and then account for that when you do your reconstruction."

The primary challenge in OCT is the shallow depth of tissue that coherent light can penetrate. The team at Carnegie Mellon has focused its recent work on increasing this penetration. Farkas and his associates have been examining the use of fast-optical-coherence gated imaging at relatively long wavelengths—around 1300 nm. Such long wavelengths decrease scattering while improving coherent interference. Studies done on mouse skin and brains have indicated that longer wavelengths improve both penetration and contrast. "It becomes more important to go to the near-infrared as you are trying to go deeper because scattering is very wavelength dependent—and scattering is what really kills you," says Farkas. Ultimately, he says, the best answer may be to image at several wavelengths.

CONCLUSION

While the hurdles to optical diagnostics may be significant, there is a general consensus that they are not insurmountable. Reynolds, like his fellow researchers, accepts the fact that the development of any new technology takes time. "I'm sure x-ray mammography must have gone through something like this," he says.

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Photos courtesy of Carnegie Mellon University (Pittsburgh)

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